#434 Evaluation of AFP Expression as a Predictive Marker for Response to anti-VEGFR-2 Inhibition

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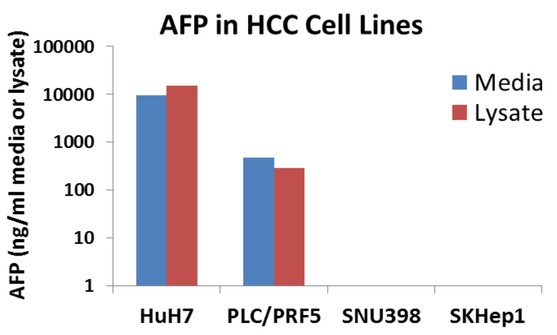
Introduction

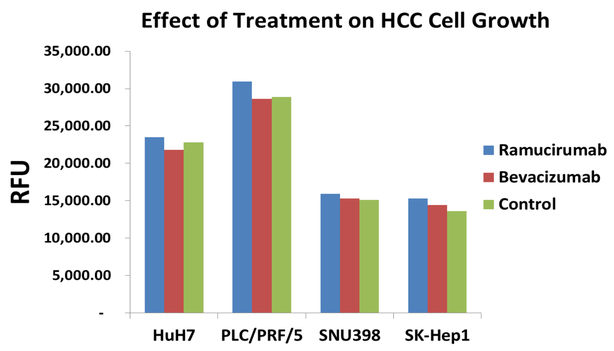
- ❖ Ramucirumab did not significantly improve survival as second line therapy in patients with advanced hepatocellular carcinoma (HCC) following first-line therapy with sorafenib in REACH Phase 3 study*.
- ❖ A pre-specified subgroup analysis showed an overall survival improvement with ramucirumab in the patient population with a baseline α-fetoprotein (AFP) level of 400 ng/mL or greater.
- ❖ Any mechanistic relationship between baseline AFP level and response to anti-angiogenic therapy (ramucirumab) in HCC is not well understood
- ❖ Xenograft and cell-line studies were performed to explore the potential relationship between AFP and inhibition of angiogenesis.

Methods

- ❑ In vivo xenograft studies were performed using four human HCC cell lines (HuH-7, PLC/PRF/5, SNU-398 and SK-Hep-1).
- ❑ DC101, a rat surrogate for ramucirumab that specifically targets mouse VEGFR-2, was used for the xenograft models.
- ❑ Expression of 44 human and mouse angiogenesis-related growth factors were evaluated using Luminex based multi-analyte profiling in the HCC cell lines.
- ❑ CRISPR, shRNA and siRNA techniques were used in gene silencing experiments.

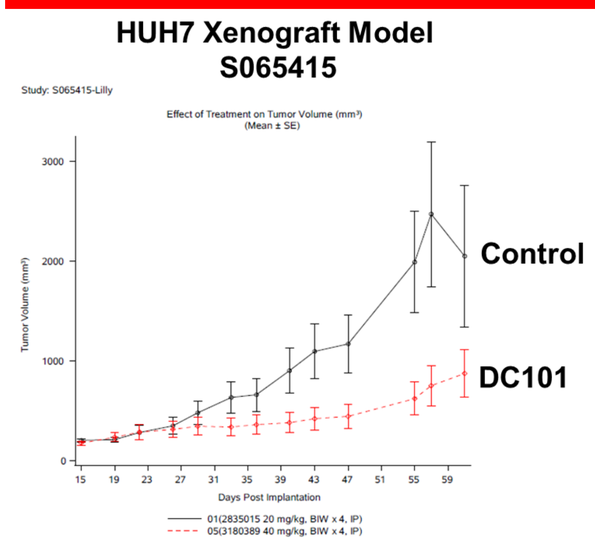
1. Differential Expression of AFP in HCC cell lines with No Anti-proliferative Effect of Anti-VEGF/VEGFR2 Treatment *In Vitro*

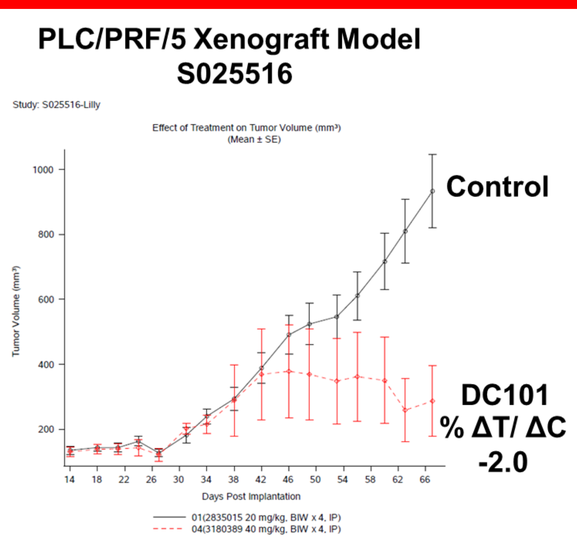




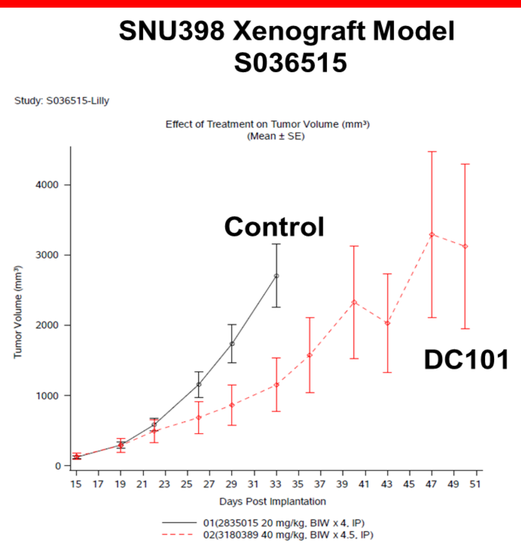
- **HuH7 and PLC/PRF5 cells expressed AFP (High AFP). SNU398 and SKHep1 had no detectable AFP expression (Negative AFP).**
- **Treatment of HCC cell lines with anti-VEGF or anti-VEGFR2 antibodies did not inhibit tumor growth *in vitro.***

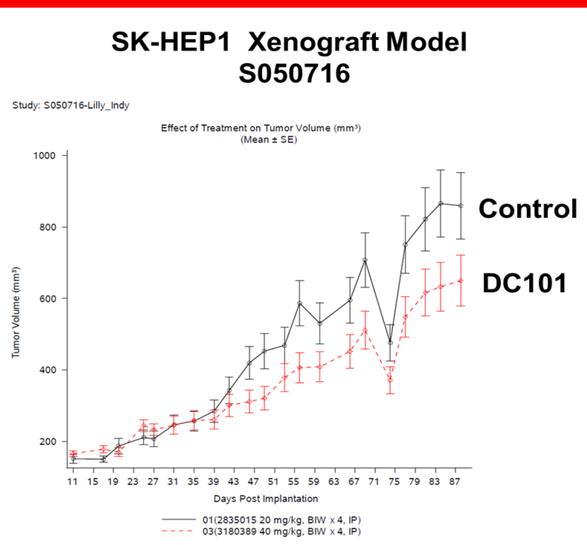
2. DC101 Inhibited Tumor Growth Xenograft Models with High AFP - Huh7 and PLC/PRF/5



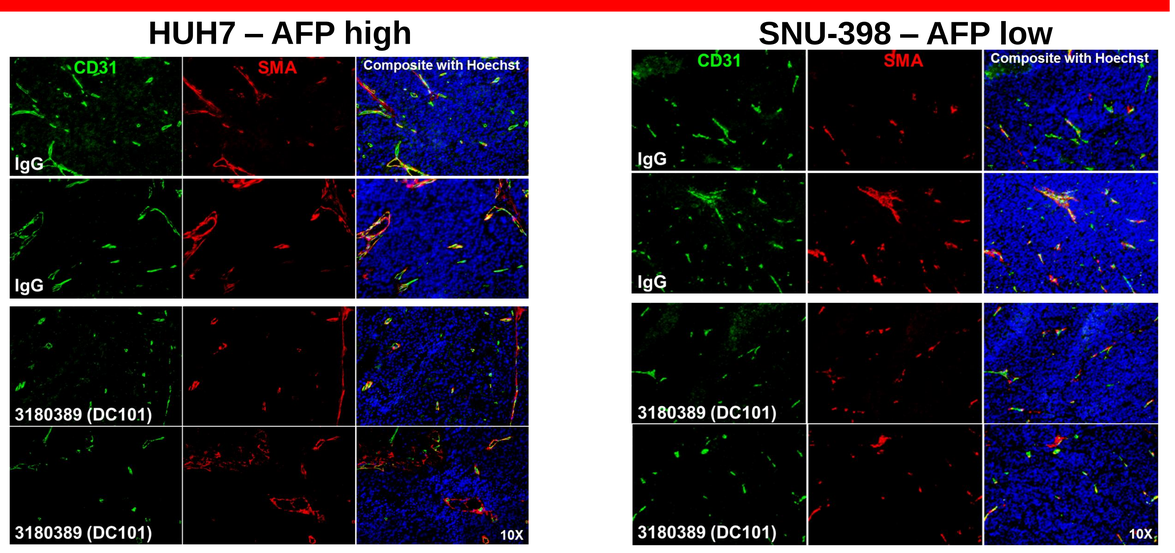


3. DC101 treatment less effective in Xenograft Models Negative for AFP - SNU398 and SK-HEP1

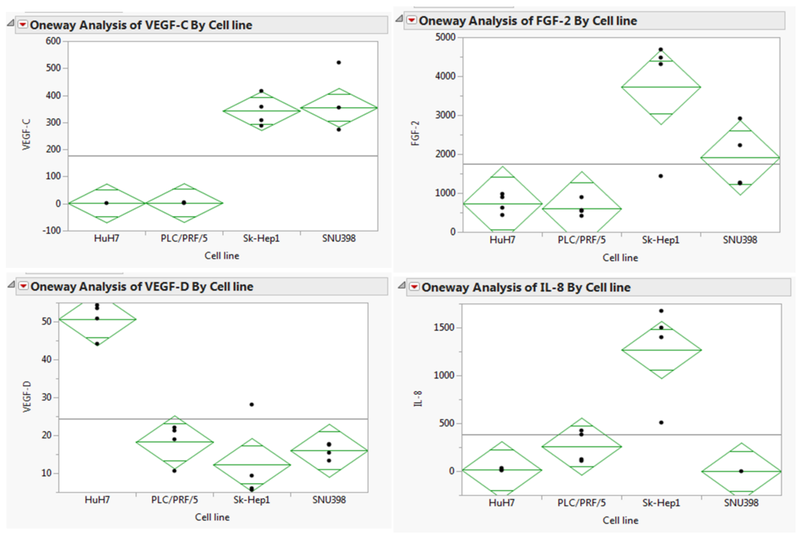




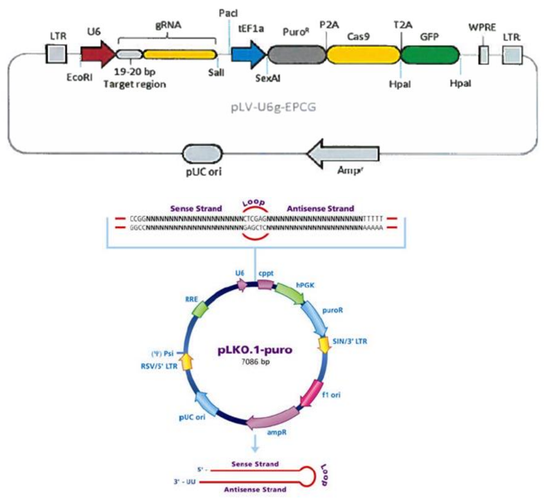
4. DC101 Inhibits Blood Vessels in Both AFP High and AFP Negative Tumor Models

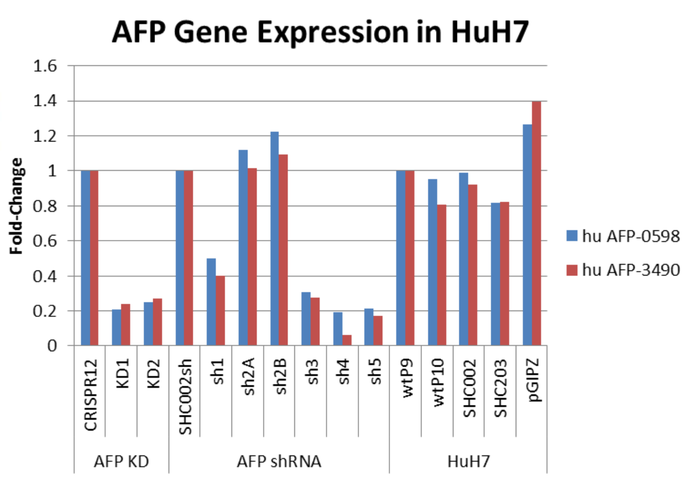


5. Differential Expression of Growth Factors in AFP High and AFP Negative Cell Lines



6. Silencing of AFP Reduced Cell Viability





Conclusions

1. DC101 inhibited tumor growth in very high AFP HuH-7 and high-AFP PLC-PRF/5 xenograft models, whereas in the AFP negative SNU-398 and SK-Hep-1 xenograft models, mice treated with DC101 exhibited progressive disease.
2. Histological evaluation indicated that DC101 effectively reduced tumor vessels in both very high AFP (HuH-7) and AFP negative (SNU-398) xenografts.
3. Differential expression of growth factors in AFP expressing vs non-AFP expressing cells was observed, including VEGF-C, VEGF-D, FGF-2 and IL-8. Similar correlations with up to 26 cell lines was observed with bioinformatics analysis.
4. Silencing of AFP reduced the viability of AFP high Huh-7 cells, suggesting that AFP may play a role in regulating cell proliferation in HCC.
5. Potential future studies include confirmation of these findings in patient derived xenograft models.
6. These studies offer initial mechanistic insights into the efficacy of ramucirumab in HCC patients with high AFP levels, an area of high unmet clinical need.

References

1. Zhu AX et al. Lancet Oncology 2015, Vol 16. 859-870.

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